PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING

PCT

To:
LEE, Won-Hee

8th Fl., Sung-ji Heights II, 642-16 Yoksam-dong, Kangnam-ku, 135-080 Seoul, republic of Korea

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)* 08 NOVEMBER 2004 (08.11.2004)

Applicant's or agent's file reference
3FPO-06-09

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/months/year)*
PCT/KR2003/001534	**30 JULY 2003 (30.07.2003)**	09 AUGUST 2002 (09.08.2002)

Applicant

KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY et al

1. The applicant is hereby notified that International Preliminary Examining Authority transmits here with the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report(but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details in the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer

COMMISSIONER

Telephone No. 82-42-481-5231

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference 3FPO-06-09	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. **PCT/KR2003/001534**	International filing date *(day/month/year)* **30 JULY 2003 (30.07.2003)**	Priority date *(day/month/year)* 09 AUGUST 2002 (09.08.2002)

International Patent Classification (IPC) or national classification and IPC

IPC7 C07D 405/12

Applicant

KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
05 MARCH 2004 (05.03.2004)	03 NOVEMBER 2004 (03.11.2004)
Name and mailing address of the IPEA/KR Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer LEE, Mi Jeong Telephone No. 82-42-481-5601

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR2003/001534

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1 - 80 , as originally filed
pages _____ , filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statment) under Article 19
pages _____ , filed with the demand
pages 81 - 89 , filed with the letter of 12/10/2004

☐ the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application(under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide** and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained inthe international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☒ the claims, Nos. 4, 5, 11

☐ the drawings, sheet _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed." and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION

International aplication No.
PCT/KR2003/001534

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1 - 3, 6 - 10	YES
	Claims		NO
Inventive step (IS)	Claims	1 - 3, 6 - 10	YES
	Claims		NO
Industrial applicability (IA)	Claims	1 - 3, 6 - 10	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are referred to in this report:

D1: J. Pharmacol. Exp. Ther. Vol.201(3), pp.1184-1192 (2001)
D2: J. Med. Chem. Vol.42(18), pp.3711-3717 (1999)
D3: US 5837702 A (17 Nov. 1998)
D4: J. Med. Chem. Vol.40(1), pp.24-34 (1997)
D5: US 5629429 A (13 May 1997)

1. Novelty

The present invention relates to benzopyran derivatives substituted with secondary amines including an imidazole (formula 1), their preparation, and pharmaceutical compositions containing them. The pharmaceutical compositions are (1) useful for treatment of cancer, rheumatoid arthritis, and diabetic retinopathy through anti-angiogenic properties (claim 8), (2) useful as neuroprotectives for prevention and treatment of infant asphyxia, glaucoma, diabetic neuropathy, and head trauma (claim 9), (3) useful as anti-oxidants for prevention and treatment of neurodegenerative diseases including aging, senile dementia, and atherosclerosis (claim 10).

D1-D5 disclose benzopyran derivatives substituted with secondary amines including an imidazole useful as cardiovascular agents.

The compound of formula 1 in the present invention differs from the benzopyran derivatives in D1-D5 in that the substituent R2 is "dimethoxymethyl" while the corresponding substituents in D1-D5 are "methyl"s.

Therefore, claims 1-3 and claims 6-10 of the present invention can be considered to be novel over D1-D5 [Article 33(2) PCT].

2. Inventive Step

Although the chemical structures of benzopyran derivatives in D1-D5 are so close to that of formula 1 in the present invention, their medical use is quite different from that of formula 1 and there is no indications or suggestions in D1-D5 to lead those who skilled in the art to expect

(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of:

Box V.

that the compound of formula 1 would show anti-angiogenic, neuroprotective, and anti-oxidant activities by changing the "methyl" substituent with "dimethoxymethyl".

Therefore, the inventive step of the present invention can be acknowledged over D1-D5 [Article 33(3) PCT].

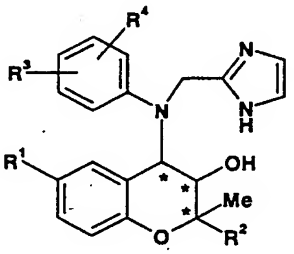
3. Industrial Applicability

The subject-matter of claims 1-3 and claims 6-10 appears to be industrially applicable [Article 33(4) PCT].

WHAT IS CLAIMED IS :

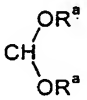
1. (currently amended) Benzopyran derivatives substituted with secondary amines including imidazole by the following formula 1, their stereochemical isomers and their pharmaceutically acceptable salts.

FORMULA 1



Wherein,

R^1 represents H, CN, NO_2 or NH_2,

R^2 represents  wherein R^a represents straight or branched alkyl group of C_1-C_4,

R_3 and R_4 are independent each other and represent H, Cl, Br, F, alkyl group of C_1-C_3, OR^b, CF_3, OCF_3, NO_2, or CO_2R^b; R^b represents H or alkyl group of C_1-C_3,

and * represents the chiral center.

2. Benzopyran derivatives substituted with secondary amines including imidazole, their stereochemical isomers and their pharmaceutically acceptable salts according to claim 1, wherein the compound of formula 1 is selected from the

group consisting of:

1) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

2) (2S,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

3) (2R,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

4) (2R,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

5) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-trifluoromethylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

6) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-methoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

7) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-trifluoromethoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

8) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-bromophenyl)-

N-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

9) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(2,4-dimethylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

10) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(2-isopropylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

11) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(2,3-dimethylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

12) (2R,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(2,3-dimethylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

13) (2R,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-bromophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

14) (2R,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-methoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

15) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-fluorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

16) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(2-methoxyphenyl)-

N-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

17) (2R,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(2-isopropylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

18) (2R,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(2-methoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

19) (2R,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(3-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

20) (2S,3S,4R)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(3-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

21) (2R,3R,4S)-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-4-[*N*-(4-trifluoromethoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

22) (2S,3S,4R)-6-cyano-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

23) (2R,3R,4S)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

24) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-chlorophenyl)-

N-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

25) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-trifluoromethylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

26) (2R,3R,4S)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-trifluoromethoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

27) (2R,3R,4S)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(2,3-dimethylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

28) (2R,3R,4S)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-methoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

29) (2R,3R,4S)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-bromophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

30) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(2,3-dimethylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

31) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(2-methoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

32) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-methoxyphenyl)-

N-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

33) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(2,4-dimethylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

34) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(2-isopropylphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

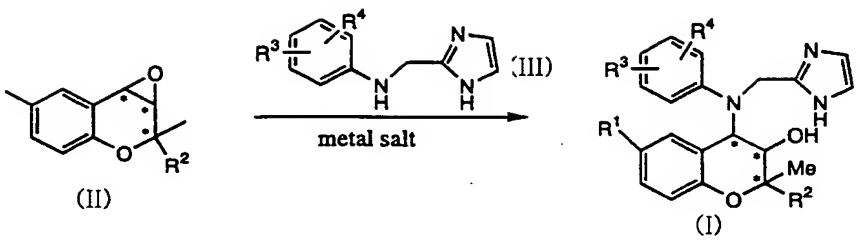
35) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-trifluoromethoxyphenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran;

36) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-bromophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran; and

37) (2S,3S,4R)-6-amino-3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-4-[*N*-(4-fluorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-2*H*-1-benzopyran.

3. (previously amended) A process for preparing the benzopyran derivatives substituted with secondary amines including imidazole of claim 1, comprising the step of reacting an epoxide compound (II) with a secondary amine compound including imidazole (III) in the presence of a metal salt in an reaction solvent to obtain a compound (I), as described in scheme 1.

Scheme 1



Wherein R_1, R_2, R_3, R_4 * and n are each defined as above claim 1, the metal salt is selected from the group consisting of $Mg(ClO_4)_2$, $CoCl_2$, $LiClO4_2$, $NaClO_4$, $CaCl_2$, $ZnCl_2$, $LiBF_4$ and $Zn(Tf)_2$, and the reaction solvent is selected from the group consisting of acetonitrile, tetrahydrofuran and dimethylformamide.

4. (previously deleted)

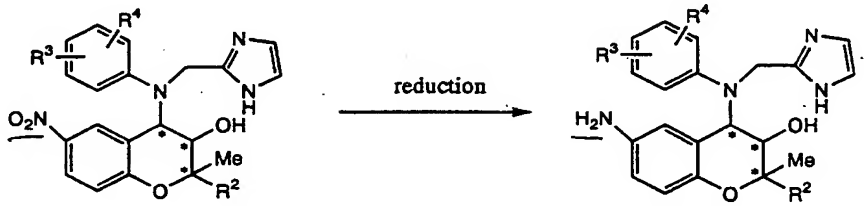
5. (previously deleted)

6. A process for for preparing the benzopyran derivatives substituted with secondary amines including imidazole of claim 1, comprising the step of

1) reduction of the nitro compounds (IV) by hydrogenation using metal catalysts such as platinum, palladium, palladium on carbon (Pd/C), Raney-nickel, etc. in a suitable solvent, to obtain the amino compound (V) as described in scheme 4, below; or

2) reduction of the nitro compounds (IV) using an reducing agent in the presence of $CuSO_4$, $Cu(OAc)_2$, $CoCl_2$, $SnCl_2$ or $NiCl_2$, to obtain the amino compound (V) as described in scheme 4, below.

Scheme 4



(IV) (V)

Wherein R^2, R^3, R^4 and * are each defined as above claim 1.

7. The process according to claim 6, wherein the reducing agent is $NaBH_4$.

8. Pharmaceutical compositions pharmacologically useful for treatment of cancer, diabetic retinopathy, and rheumatoid arthritis by suppressing angiogenesis, which contain the benzopyran derivatives substituted with secondary amines including imidazole of claim 1 or their pharmaceutical acceptable salts as an active ingredient.

9. Pharmaceutical compositions pharmacologically useful as neuroprotectives for prevention and treatment of infant

asphyxia, glaucoma, diabetic neuropathy, and head trauma, which contain the benzopyran derivatives substituted with secondary amines including imidazole of claim 1 or their pharmaceutical acceptable salts as an active ingredient.

10. Pharmaceutical compositions pharmacologically useful as anti-oxidants for prevention and treatment of neurodegenerative diseases including aging, senile dementia, and atherosclerosis, which contain the benzopyran derivatives substituted with secondary amines including imidazole of claim 1 or their pharmaceutical acceptable salts as an active ingredient.

11. (currently deleted)